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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/282,879	03/31/1999	SUBROTO CHATTERJEE	46906-2-DIV	9227

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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/282,879	CHATTERJEE, SUBROTO	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 13-17 and 31 are now currently pending in this application.

Drawings

This application has been filed with drawings that have been accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 15-17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13, 15-17 are rejected because of the recitation of the phrase "or derivative thereof". While Examiner acknowledges that the specification defines fragments or derivatives as proteins or polypeptides which retain the biological activity of sphingomyelinase (SM), the specification does not define what the metes and bounds of the term "derivative" are. That is to say, whether the derivative is any protein from any source with the same activity or must the protein have some amount of structural homology to SEQ ID NO:2? And if so how much homology must be present to be a derivative? Therefore, the claim as written does not convey the scope of "derivatives" encompassed rendering the claim unclear.

In response to the above rejection, applicants have traversed the above rejection. However, they have amended the claim to show that the fragments and derivatives have at least

50% of the activity of the polypeptide with SEQ ID NO:2. While the above amended does provide the activity of the fragment and derivative, the question of its structural homology to SEQ ID NO:2 has been left unanswered. Examiner has noted that applicants have filed a new claim addressing the structural relation of the fragment or derivative to SEQ ID NO:2. Amending claim 1 to include such relation to SEQ ID NO:2 would overcome this rejection. Until such time the claim as written does not convey the scope of "derivatives" encompassed rendering the claim unclear. Hence the above rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13 and 15-17 are directed to polypeptide derivatives corresponding to the sequence of SEQ ID NO:2. Claims 13 and 15-17 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, (modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2) that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences

encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the claimed genus of derived polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2, within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the above rejection applicants have traversed the above rejection arguing that Examiner's position that the application discloses only a single species of the claimed genus is simply untrue and that applicants have disclosed "***many acceptable enzymes fragments and derivatives***" and provide a list of pages and line numbers where they have disclosed them. Examiner respectfully disagrees with applicants argument. First of all, applicants allegation that "Examiner's position that the application discloses only a single species of the claimed genus is simply untrue" is baseless. Furthermore, a perusal of the reference points which applicant provides as places where they have disclosed many acceptable enzymes are simply disclosures of

the single amino acid sequence which they have described. For example, applicants state that they have described the species in page 7, lines 19-26 which is as follows,

> "We have now isolated cDNA encoding a human N-Smase. The cDNA is represented by SEQ ID NO:1 (Figure 1) and encodes a protein that when expressed in *E.coli* cells has an apparent molecular weight of 44 Kda as determined by polyacrylamide gel electrophoresis using sodium laurylsarcocine. That recombinant protein is bound by an antibody against the 92 kDa native N-Smase. Protein was also expressed in Cos-7 cell. The isolated and purified recombinant N-Smase has been shown to have N-Smase activity. See, for instance the results disclosed in Example 1 which follows".

It can be seen that nowhere in this paragraph applicants have disclosed at least a representative number of species of derivatives or fragments of SEQ ID NO:2. Next, applicants also point out to figures 1 and 2 which again simply provide the nucleotide and the amino acid sequences respectively of a single N-Smase. Applicants reference to other pages in the disclosure also does not provide support for fragments and derivatives such that it would satisfy written description requirements. Thus, it is clear that applicants do not have ample support for derivatives and fragments in their specification.

As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the

species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera of claims 13 and 15-17 includes species which are widely variant in structure. The genus Claims 13 and 15-17 is structurally diverse as it encompasses polypeptides with structural similarity to SEQ ID NO:2 as well as which lack any such similarity but are capable of N-SMase activity. As such, neither the description of the structure and function of SEQ ID NO:2 nor the disclosure solely of functional features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-17 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatterjee et al. (J. Biol. Chem., 1989, Vol. 264(21):12554-12561), Ogita et al. (WO 9518119, 7-6-1995) and Ausubel et al. (Current Protocols in Molecular Biology, John Wiley and Sons, 1987, pages 10.0.3-10.0.6). Claims 13-17 and 31 in this instant application are drawn to a method of identifying a compound which when used in a reaction comprising sphingomyelin as the substrate, the neutral sphingomyelinase as the enzyme and ceramide as the cleaved product, leads to reduced concentration of the cleavage product such that the identified compound could be used in the diagnosis or treatment of human neutral sphingomyelinase related disorder.

Chatterjee et al. teach an assay method for the activity of neutral sphingomyelinase wherein a mixture of sphingomyelin is treated with the enzyme sphingomyelinase under conditions wherein the substrate is cleaved and cleaved product, ceramide is detected (see page 12555, 2nd column). Chatterjee et al. also teach that sphingomyelinase catalyzes the hydrolysis of sphingomyelin to ceramide and phosphorylcholine at both acidic and neutral pH. The reference also teaches that the study of neutral sphingomyelinases are necessary in view of its involvement in gentamicin-mediated nephrotoxicity in man and also due to the involvement of sphingosine, released as a consequence of the action of sphingomyelinase, in a cascade of reactions leading to the regulation of protein kinase C activity (see page 12554, Introduction). Thus it appears that the substrate, cleavage product and the importance of the sphingomyelinase reaction was common knowledge in the art. However, while the above reference teaches a purified SM and an assay for its activity, it does not teach a recombinant SM or the use of recombinant SM in an assay for detection of a pharmacological agent even though the activity assay for the purified enzyme could be used for the same.

Ogita et al. teach the manufacture of a sphingomyelinase inhibitor obtained from a microorganism and its use to treat a variety of diseases and disorders such as HIV, diabetes, leukemia, cachexia etc. Ogita et al. also teach an assay for determining the inhibitory activity of a compound using sphingomyelinase isolated from a rat brain wherein the assay is performed at a pH of 7.5 very close to the neutral pH. However, this reference also does not teach the use of recombinant SM.

Ausubel et al. in their voluminous manual teach all the techniques related to cloning a known protein starting from its purification stage up to obtaining its cDNA and the recombinant form of the protein. Examiner draws the attention of the applicant to the enclosed pages 10.0.3-10.0.6 wherein the reference teaches how one can obtain the oligonucleotide probe from a purified protein. Other chapters in the book also teach how one skilled in the art can make a specific cDNA library and use the oligonucleotide probe to clone the specific protein and obtain it in the recombinant form.

With the purified SM as taught by Chatterjee et al. and the knowledge existing in the art of protein biochemistry and molecular biology to make recombinant proteins and the importance of sphingomyelinase inhibitors as taught by Ogita et al., it would have been obvious to one skilled in the art at the time the invention was made to use the purified protein of Chatterjee et al., obtain a cDNA clone and make recombinant sphingomyelinase using the techniques of Ausubel et al. and use it to develop a method of identifying other compounds which inhibit sphingomyelinase on line with Ogita et al. such that compounds could become useful in diagnosis or treatment of a human neutral sphingomyelinase related disorder. Chatterjee et al. teach that one of ordinary skill in the art would be motivated to do this in order to study the

biochemical mechanisms involved in gentamicin-mediated nephrotoxicity or in Niemann-Pick disease and Ogita et al. teach that one of ordinary skill in the art would be motivated to do this because, when the transmission of signals introduced by IL-1beta and TNF-alpha is blocked by inhibiting the activity of sphingomyelinase using an inhibitor, the symptoms of various diseases related to cytokines can be improved. One would have a reasonable expectation of success since Chatterjee et al. provide a purified sphingomyelinase and a robust and time tested assay method and Ogita et al. provide an assay and demonstrate the existence of a chemical compound which inhibits sphingomyelinase and Ausubel et al. provide time tested recombinant techniques that has been used by a number of other inventors.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicant has traversed the above rejection of claims 13-17 arguing that PTO has not pointed to anything in the cited references that shows how to make the cDNA clone and merely relies on Ausubel for general reference information. Applicants also argue that Office assumes that it would be obvious to make and use a cDNA library to obtain the cDNA and no protein or nucleic acid sequence has been cited by the PTO that would allow one to perform these steps, particularly the step of making suitable probes. Examiner respectfully disagrees with such arguments. There is no need for the Examiner to provide references which disclose amino acid or nucleic acid sequences to support the rejection. This is because contrary to applicants argument, the art has advanced so much that the availability of purified protein is enough for one skilled in the art to identify the nucleic acid encoding such protein and obtain a recombinant protein. The procedures may be painstaking for

some proteins, but still it can be achieved. Furthermore, even if the N-terminal of the polypeptide is blocked and obtaining the amino acid sequence is difficult the art provides robust alternate methods which can be adapted in such cases to arrive at the cDNA clone. One such alternate method is the expression cloning method using λgt vectors.

Next, applicants state that it is the object of their invention to provide protein and nucleic acid sequences information that would allow a worker to make and use the recombinant enzyme of the claimed method. Examiner disagrees that the invention is so broad. On the contrary the present invention is simply drawn to a method of identifying a compound which modulates the activity of N-Smase and use such compound in diagnosis or treatment of N-Smase related disorders.

Applicants again try to take refuge in *In re Deuel* and *In re Bell* even though Examiner has already explained as to why those judgments do not apply to instant claims. Examiner refers the applicant to peruse arguments in the previous Office action. Applicants also allege that Examiner has used a post-dated reference in the rejection which is simply untrue. Examiner has used the post-dated reference as an evidence document in order to further lend support that the amino acid sequence reported in the post-dated reference is actually in deed that of N-Smase that was purified by Chatterjee et al. reference used in the rejection. Therefore applicants argument that the Examiner has used a post-dated reference in the rejection while the reference was actually used in the arguments is misplaced.

Applicants further argue that the English translation of Ogita et al. reports a bacterial sphingomyelinase inhibitor and the assay provided was limited to the analysis of that compound and that the reference does not teach or suggest the claimed invention when taken alone or in

combination with other references. Examiner respectfully disagrees. Ogita et al. even if it is directed to an assay involving bacterial enzyme and even if there is an understanding in the art that bacterial sphingomyelinase and human sphingomyelinases are different (which is expected), does provide the teaching that sphingomyelinase inhibitors exist in the art and that such compounds can be identified and used to diagnose and treat a number of human ailments. If not anything, the reference provides the motivation to one skilled in the art to identify compounds which modulate the activity of sphingomyelinases.

Finally applicants point out the advantages of using the recombinant enzyme which is true but is not persuasive to overcome the above invention.

Applicants have also filed an unsigned declaration by the inventor to show the Examiner as to how difficult it was to clone the above enzyme by following the traditional route and techniques and he had to resort to expression cloning methods. However, first of all Examiner would like to point out that the declaration is unsigned and even if it were signed, the declaration is not persuasive to overcome the above rejection because it is well recognized in the art that some proteins whose N-terminal is blocked poses problems for sequencing and that one has to resort to other methods such as expression cloning using λgt vectors. Such techniques are well known in the art and described by Ausubel et al.

Applicants appear to be ignoring an important point in all their arguments. Applicants are unable to show that the recombinant form and the natural enzyme are not one and the same. Until such time applicants can clearly point out, beyond any doubt, that the recombinant enzyme exhibits certain unique properties which the natural enzyme does not and only because of such unique properties it can be used for identifying compounds which modulate its activity, the

above references render the instant invention *prima facie* obvious and hence Examiner continues to maintain the above rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Manjunath N. Rao. Ph.D.
11/22/02